

## **Dose Response and Concentration Response Analysis of Drug Effects**

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## **Dose-Effect Relationship**

The intensity and duration of a drug's effects are a function of the drug dose and drug concentration at the effect site

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## **Monitoring Dose-Effect**

### **Level**

- **Molecular (e.g, enzyme inhibition)**
- **Cellular (*in vitro* tissue culture, blood cells)**
- **Tissue or organ (*in vitro* or *in vivo*)**
- **Organism**

**Endpoint used to measure effect may be different at each level**

**Overall effect = sum of multiple drug effects and physiological response to drug effects**

## **Endpoints to Monitor Drug Effect**

### **Farnesyltransferase Inhibitors for Cancer**

<b>LEVEL</b>	<b>ENDPOINT</b>
<b>Molecular</b>	<b>Farnesyltransferase inhibition</b>
<b>Cellular</b>	<b>Proliferation rate, apoptosis</b>
<b>Tumor</b>	<b>Response (change in tumor size)</b>
<b>Organism</b>	<b>Survival, quality of life</b>

## **Dose-Effect Endpoints**

**GRADED**      **Continuous scale ( $\uparrow$ dose  $\rightarrow$   $\uparrow$  effect)**

**Measured in a single biologic unit**

**Relates dose to intensity of effect**

**QUANTAL**      **All-or-none pharmacologic effect**

**Population studies**

**Relates dose to frequency of effect**

## Erythropoietin and Anemia

Chart showing peak hematocrit increment (%) over Erythropoietin Dose [units/kg]  
Example of Dose-Effect curve.

**Eschbach et al. NEJM 316:73-8, 1987**

# Drug-Receptor Interactions

Graphic illustration of drug-receptor complex with ligand-binding and effector domains.

$$\text{Effect} = \frac{\text{Maximal effect} \times [\text{Drug}]}{K_D + [\text{Drug}]}$$

( $K_D = k_2/k_1$ )

## Dose-Effect Relationship

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Effect = Maximal effect if  $[\text{Drug}] \gg K_D$

# Graded Dose-Effect Curve

Chart showing % of Maximal Effect over Drug concentration.

Graphic illustration of  $EC_{50}$ .

# Log Dose-Effect Curve

Chart showing % of maximal effect over log drug concentration.

Graphic illustration of  $EC_{50}$ .

# Lidocaine Graded Dose-Effect

Chart showing analog pain score over Lidocaine blood level [ $\mu\text{g/ml}$ ]

**Ferrante et al. Anesth Analg 82:91-7, 1996**

# Theophylline Dose-Effect

Chart showing % control over Theophylline [ $\mu\text{M}$ ] for bronchial smooth muscle relaxation and PDE inhibition.

**Rabe et al. Eur Respir J 8:637-42, 1995**

# Theophylline Pharmacodynamics

Graph indicating FEV<sub>1</sub> (% normal) over Theophylline [mg/L] with E<sub>MAX</sub> = 63% and EC<sub>50</sub> = 10 mg/L

**Mitenko & Ogilvie NEJM 289:600-3, 1973**

# Metformin Dose-Response

Chart showing decrease in FPG from placebo [mg/dl] and decrease in HbA from placebo (%) over dose [mg/d]

**Garber et al. Am J Med 102:491-7, 1997**

# Dose-Effect Parameters

**POTENCY: The sensitivity of an organ or tissue to the drug**

**EFFICACY: The maximum effect**

## Comparing Dose-Effect Curves

Chart showing % of maximal effect over [Drug] for Drugs A, B, and C. Illustration of different potency and efficacy.

$$\text{Effect} = \frac{\text{Maximal effect} \times [\text{Drug}]}{K_D + [\text{Drug}]}$$

# Thiopurine Cytotoxicity

Chart showing % cytotoxic effect over Thiopurine [M] (thioguanine and mercaptopurine).

**Adamson et al. Leukemia Res 18:805-10, 1994**

# Thiopurine Metabolic Activation

Chemical structures

# Oral Mercaptopurine

Chart indicating MP AUC [ $\mu\text{M} \times \text{hr}$ ] over MP Dose ( $\text{mg}/\text{M}^2$ ).  $\text{AUC} = \text{Dose} \times \text{F}$   
Clearance

**Balis et al. Blood 92:3569-77, 1998**

# Receptor-Mediated Effects

Chart showing % maximum effect over [Drug] for agonist, partial agonist and antagonist

# Drug Interactions

Chart showing % of maximal effect over [Drug] for agonist, agonist + competitive antagonist, and agonist + non-competitive antagonist

## Graded Dose-Effect Analysis

**Identify the therapeutic dose/concentration**

**Define site of drug action (receptor)**

**Classify effect produced by drug-receptor interaction (agonist, antagonist)**

**Compare the relative potency and efficacy of drugs that produce the same effect**

**Assess mechanism of drug interactions**

## Quantal Dose-Effect Distribution

Frequency histogram of subjects responding to threshold dose in a population.

# Cumulative Dose-Effect Curve

Cumulative % of subjects responding over dose

## Cumulative Dose-Effect Study

<b>Dose Level</b>	<b>No. of Subjects</b>	<b>No. Responding</b>	<b>% Response</b>
<b>1</b>	<b>10</b>	<b>0</b>	<b>0</b>
<b>2</b>	<b>10</b>	<b>1</b>	<b>10</b>
<b>3</b>	<b>10</b>	<b>3</b>	<b>30</b>
<b>4</b>	<b>10</b>	<b>5</b>	<b>50</b>
<b>5</b>	<b>10</b>	<b>7</b>	<b>70</b>
<b>6</b>	<b>10</b>	<b>8</b>	<b>80</b>
<b>7</b>	<b>10</b>	<b>9</b>	<b>90</b>
<b>8</b>	<b>10</b>	<b>10</b>	<b>100</b>

# Therapeutic and Toxic Effects

Chart showing % responding over dose for therapeutic and toxic effects.

Graphic illustration of ED<sub>50</sub>, ED<sub>99</sub>, TD<sub>1</sub> and TD<sub>50</sub>.

## Therapeutic Indices

$$\text{Therapeutic Ratio} = \frac{\text{TD}_{50}}{\text{ED}_{50}} = 2.5$$

$$\text{Certain Safety Factor} = \frac{\text{TD}_1}{\text{ED}_{99}} = 1.3$$

$$\text{Standard Safety Margin} = \frac{\text{TD}_1 - \text{ED}_{99}}{\text{ED}_{99}} \times 100 = 31\%$$

## **Digoxin Therapeutic Index**

**Digoxin (single oral dose,  $\mu\text{g}/\text{kg}$ ) showing ventricular slowing for 90% of patients and vomiting for 55% of patients**

## Doxorubicin Cardiotoxicity

Chart showing probability of CHF over total doxorubicin dose [mg/m<sup>2</sup>]

**von Hoff et al. Ann Intern Med 91:710-7, 1979**

## Lidocaine Quantal Dose-Effect

Chart showing % achieving complete analgesia over total lidocaine dose (mg)  
ED<sub>50</sub> = 400 mg, ED<sub>90</sub> = 490 mg

**Ferrante et al. Anesth Analg 82:91-7, 1996**

## Antihypertensive Dose-Effect

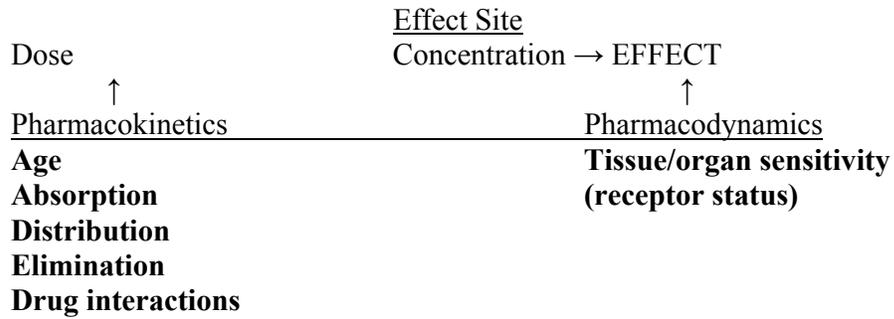
Drug	Dose Range [mg]		Lowest Effective Dose [mg]
	Early Studies	Present Dose	
Propranolol	160-5000	160-320	80
Atenolol 1	00-2000	50-100	25
Hydrochlorthiazide	50-400	25-50	12.5
Captopril	75-1000	50-150	37.5
Methyldopa	500-6000	500-3000	750

Johnston Pharmacol Ther 55:53-93, 1992

# Antihypertensive Drugs

Chart showing % with maximal effect over log dose showing desirable dose range, dose range most often used, and adverse effects.

## Relating Dose to Effect *In Vivo*



## Effect Compartment (PK/PD Model)

Graphic illustration of a 2-compartment PK model with an effect compartment (PK/PD).

## Concentration and Effect vs. Time

Chart showing Non-steady state - Conc./Amount over time in central, peripheral, and effect compartments.

# Pharmacodynamic Models

## Fixed effect model

**Linear model**      Effect =  $E_0 + S \times [\text{Drug}]$

**Log-linear model** Effect =  $I + S \times \text{Log}([\text{Drug}])$

## **E<sub>max</sub> model**

Sigmoid E<sub>max</sub> model

$$\text{Effect} = \frac{E_{MAX} \times [\text{Drug}]^H}{EC_{50} + [\text{Drug}]^H}$$

## Sigmoid $E_{\max}$ PD Model

Two graphs, both indicating effect (%) over drug. The graph on the left indicates  $H = 5$ ,  $H = 2$ ,  $H = 1$ ,  $H = 0.5$  and  $H = 0.1$  with  $EC_{50}$  equal for all. The graph on the right indicates  $EC_{50}$  on log scale.

Hysteresis and Proteresis Loops

Intensity of drug effect over plasma drug concentration

# Role of Dose-Effect Studies

## **Drug development**

Site of action

Selection of dose and schedule

Potency, efficacy and safety

Drug interactions

## **Patient management**

Therapeutic drug monitoring

**Risk-benefit (therapeutic indices)**